Statins – are they potentially useful in rheumatology?

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Abstract: For more than 30 years statins have been successfully used in patients with hypercholesterolemia and cardiovascular diseases. Recently, there is a growing body of evidence, that statins exert effects by much exceeding the effect of cholesterol level decrease. Inhibition of earlier stages of cholesterol biosynthesis pathway (not influencing the very cholesterol level) results in blocking the intermediate metabolite synthesis; isoprenoids (farnesyl phosphate and geranyl phosphate), which play a regulatory function in cells. Statins have antiatherosclerotic, antiinflammatory, antioxidant, immunomodulatory and antithrombotic effects. It applies equally to diseases of chronic inflammation type, as to those, where bone metabolism is disturbed. It is well known that statins decrease bone fracture risk; through bone formation intensification, and inhibition of bone tissue resorption. Slowing down the atherosclerosis progression is a very important effect, considering that in rheumatoid arthritis (RA) and in systemic lupus erythematosus (SLE) we are dealing with premature and rapid progression of atherosclerotic lesions. In this paper statins pathways of action in rheumatic diseases (including pleiotropic effects), and their potential use in rheumatology have been discussed. Though there is lack of reliable data enabling statins introduction to standard complementary therapy in rheumatic diseases, the results however of completed studies allow concluding of their utility. The statins that were most frequently evaluated in clinical studies were simvastatin and atorvastatin. Studies on statins have been performed in RA, SLE, osteoporosis and systemic vasculites.

Key words: inflammatory markers, pleiotropic effect of statins, rheumatic diseases, statins

INTRODUCTION

The first statin (mevastatin), as an agent selectively inhibiting the hydroxymethylglutaryl coenzyme A reductase, and thus blocking the cholesterol synthesis and decreasing its blood concentration, was discovered in 1976 in Japan. It has not, however, been introduced to treatment because of its toxicity demonstrated in animals.

In 1987 lovastatin was registered for lipid disorders treatment in humans, in the United States. In the following years, mainly for their antiatherosclerotic effect, statins have gradually become drugs of growing popularity [1]. In 2004, statins were registered as over the counter drugs in Great Britain [2].

The significance of statins keeps rising because of their application for lipid profile improvement, as well as for the activity reaching beyond their cholesterol-lowering effects (pleiotropic properties) [3].

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Received: July 04, 2007. **Accepted in final form:** October 03, 2007.
Conflict of interest: none declared.
Pol Arch Med Wewn. 2007; 117 (9): 420-425

The preparations characteristics

The presently available statin preparations are not a homogenous group chemically, which implicates a variability of indications and limitations of their use.

There are two generations of statins, among them there are six statins, which are commonly in use. The first generation, 3 natural statins, the funghi metabolism products, lovastatin, simvastatin and pravastatin; the second generation, 3 synthetic statins fluvastatin, atorvastatin and rosuvastatin. In 2001 cerivastatin for its serious adverse reactions, was withdrawn from use.

Each statin has different pharmacokinetic properties, which causes differences in the force of hypolipemic and pleiotropic action and adverse reactions.

Hydrofilic statins, pravastatin and fluvastatin, are more liver selective, they penetrate the blood-brain barrier to a small extent and are characterized by a lesser drug penetration to other tissues. A limited penetration through cellular membranes may limit their beneficial pleiotropic effect (for example in the vascular wall), but at the same time causes a rarer occurrence of adverse reactions (in muscles and in the central nervous system).

Lipophilic statins, simvastatin, lovastatin and atorvastatin, to a greater extent than hydrophilic statins penetrate through liver cell and endothelial membrane as well as the blood-brain

barrier, which may induce a more powerful pleiotropic effect. It also causes a different adverse reaction profile.

Action mechanism

Statins are the 3-hydroxy-3-methyl-3-glutaryl coenzyme A reductase inhibitors, an enzyme, which catalyzes also the hydroxy-methyl-glutaryl co-enzyme A transformation into mevalonian.

The effect of lipid profile improvement is associated mainly with the inhibition of mevalonian production, a substrate of endogenic cholesterol synthesis.

Studies performed during recent several years have stressed the beyond lipid, pleiotropic statins effect (anti-inflammatory, antioxidant and antithrombotic) [4]. Not all mechanisms and their clinical repercussions have been sufficiently demonstrated. It is known that the cholesterol synthesis, early stages inhibition (not influencing directly the cholesterol level itself), results in the intermediate metabolites synthesis blockage; isoprenoids (farnesyl phosphate and geranyl phosphate) which play a regulatory role in cells, and thus; influences the proliferation and cell differentiation processes [5].

Indications for use of statins

So far the main indication for statins use is the increased total cholesterol and low-density lipoproteins (LDL) blood level.

According to more recent studies statins are used for more and more clinical indications [6]. In metabolic syndrome and type 2 diabetes, characterized by a lipid disorder called atherogenic dislipidemia, statin therapy improves the lipid profile and decreases apolipoprotein B level (Heart Protection Study on simvastatin [7]).

Plausible trends in statin's actions in rheumatic diseases

Regarding the statin mechanism of action, there are several potential options of this drug class that may concern rheumatic diseases such as: 1) inhibition of atherosclerosis progression and lipid profile improvement, 2) osteoporosis prevention and the influence on bone metabolism, 3) inhibition inflammation (also through immunomodulation).

Antiatheroslerotic effect

Epidemiologic evidence demonstrates that in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) there is a premature, rapidly progressing atherosclerosis development, followed by cardiovascular complications [8,9]. In a large group of patients these complications are the reason for an increased mortality and preterm disability. Classical cardiovascular risk factors such as hypercholesterolemia, do not occur more often than cardiovascular complications in these groups [10]. The opinion dominates that atherosclerosis development is associated with chronic inflammation being the basis for the development of systemic connective tissue diseases.

Atherosclerosis is a chronic inflammatory reaction to arterial endothelium damage, combined with oxidative stress, cholesterol deposition, enhanced blood coagulation and a fibroproliferative process [11]. The morphologic marker of atherosclerosis represents structural and functional vascular endothelium damage, mainly through inflammatory processes and lipoprotein metabolism disorders. There are numerous similarities in the pathomechanism of atherosclerosis and RA alteration development. In both diseases macrophage activation can be observed, the increase in tumor necrosis factor α - TNF-α level, interleukin 6 (IL-6), C-reactive protein – CRP and metalloproteinases, T cell activation and the Th1/Th2 ratio altered in favor of Th1. All these parameters are higher in RA. A greater adhesion molecules expression can be seen in endothelial cells (intercellular and vascular adhesive molecule type 1, E- and P-selectins) and neoangiogenesis. Apart from that inflammatory cytokines stimulate cholesterol LDL fraction oxidation.

It is the cardiovascular system that has been clinically evaluated as the statins activity point, so far. With increasing knowledge of the mechanism of atherogenesis , the cardiovascular disease risk level can be determined by the assessment of the vascular wall and the inflammatory process activation; although the first studies of statins were targeted at the lipid profile assessment.

The mechanisms of the antiatherosclerotic statin effect include:

1) the vascular endothelium protective effect. The increase of endothelial expression of nitric monoxide production catalyzing enzyme takes place through the Rho protein inhibition (guanosine triphosphate GTP small binding protein) and Akt, protein kinase [12]. This increases the vascular wall reactivity. Statin therapy decreases the type 1 angiotensine II receptor expression in the vascular smooth muscle cells, thus weakening the vasoconstrictive effect of angiotensin II [13]
2) anticoagulant effect. The beyond lipid effect of statins manifests itself in the inhibition of thrombogenesis stages through influence on plasma coagulation factors and platelet activation. A decrease of thrombin production is a result of decreased tissue factor expression on vascular endothelial cells and in atheromatosus plaques, and of an increased thrombomodulin expression [14]. Statins (simvastatin) disrupt platelet activation after vascular damage, through the protein degranulation inhibition [15]. A decrease in fibrinogen levels is observed
3) antioxidant effect. As a result of statin administration the lipoprotein LDL resistance to oxidation increases and the anti-oxidized LDL antibodies levels decrease [16]. The removal of free radicals and the influence on paraoxidase activity (high-density lipoprotein linked enzyme) is crucial for this mechanism of action

4) the participation of osteoprotegerin (OPG) in the development of atherosclerotic lesions still remains unclear. According to some researchers, for example Kiechl et al. [17], a high level of OPG is an independent risk factor for atherosclerotic lesions progression and cardiovascular system complications. In view of these opinions the identification of statins influence on the OPG/RANKL/RANK system, also in the Celińska-Löwenhoff et al. study [18], seems worth emphasizing. The administration of 40 mg simvastatin in patients with stable coronary artery disease resulted in a significant increase in OPG level in one month of therapy, and maintained at the same level for the following 2 months. With a slight decrease in sRANKL the OPG:sRANKL ratio has also increased and the increase lasted for 3 months of follow-up.

Statins allow to obtain the clinically important aim in primary and secondary prevention of cardiovascular diseases; atheromatosus plaque stabilization, through the above mechanisms. This effect is exerted through the weakening or suppressing of the inflammatory process, antioxidant effect, vascular endothelium protection and anticoagulant effect.

This has been demonstrated in studies with the use of angiographic methods for coronary artery atherosclerotic lesions assessment, for example the MAAS examination [19] and REGRESS [20], and in cervical arteries, for example the KAPS study [21].

The TARA study led by McCarey'a et al. [22] has demonstrated that by limiting the inflammatory process, atorvastatin enables the decrease in cardiovascular complication risk in patients with RA, a highly active autoimmune inflammatory process.

The anti-inflammatory effect of statins in rheumatic diseases

An active and chronic inflammatory process is the nature of several rheumatic diseases. Systemic connective tissue diseases provide a good example, among them 2 most common ones; RA and SLE. In rheumatoid arthritis the synovial membrane of articulations affected by the inflammatory process is a rich source of proinflammatory factors, for example TNF-α, interleukin 1 (IL-1) or IL-6, which released to the circulation maintain the inflammatory process. In these diseases, the suppression of the inflammatory process is the main aim of comprehensive treatment. In the Nogashimo et al. study [23] synoviocyte cells obtained from RA and osteoarthropathy patients underwent the effect of two kinds of statins in vitro; lipofilic fluvastatin and hydrofilic pravastatin. Synoviocyte apoptosis induction, occurring through the mevalonian transformation blockage and first of all by protein geranylgeranylation inhibition and RhoA/RhoA kinase, was demonstrated after administration of lipofilic statin. Such an effect was not demonstrated with the use of hydrophilic statin (pravastatin). A beneficial anti-iflammatory effect observed in RA patients, in this study, was not confirmed in spondyloarthropathic patients. A different disease pathogenesis and the absence of inflammatory process in the degenerative lesions may be the reason [23].

Statins inhibit the induction of several proinflammatory cytokines; TNF-α, IL-1β, IL-6 and IL-8, and they decrease the CRP level, which is an exponent of the systemic inflammatory process and an independent risk factor of cardiovascular diseases [24-26]. This occurs due to a decrease of IL-6 levels, the cytokine that stimulates CRP synthesis. The effect of CRP lowering is to be seen already after several weeks of treatment, and the extent of the decrease depends on its initial level. [26] Statins also inhibit the inducible nitric oxide synthase produced by macrophages; mainly through a decrease in protein prenylation processes.

Inhibition of monocyte inflammatory activity has been demonstrated in response to oxidized lipoproteins and it is mediated by transcriptive factors such as PPAR-γ and NFκB factor *in vitro*. [27]

Immunomodulatory effect of statins

Taking the autoimmune background of several rheumatic diseases into account, the immunomodulatory statins' action on their pathogenetic mechanisms cannot be ignored.

Inhibition of isoprenylation is responsible for the statins' immunomodulatory effect. Inducing the phenomenon of immunotolerance through the protein expression decrease in the major histocompatibility complex seems important in therapy [28].

Statins inhibit the interferon γ co-stimulation dependent expression of class II antigens of the major histocompatibility complex on the macrophages surface and inhibit the factors (co stimulating, that is CD40, CD8, CD86) on the antigen presenting cell surfaces. They decrease the cytokine production through Th1 lymphocytes (IL-2, γ interferon, TNF-α); induce cytokine release from Th2 (IL-4, IL-5, IL-10) Th0 differentiation to Th2. Apart from that statins block β_2-integrin and CD11a/CD18 molecules, thus inhibiting the adhesion and co-stimulation of leukocytes. These mechanisms have been so far demonstrated in studies performed in vitro and were not convincingly confirmed in clinical trials.

Immunomodulatory effect seems to be particularly useful in the treatment of autoimmune diseases, which is however associated with a considerable risk.

Reports on autoimmunization caused by statins provide the rationale speaking in favor of the strong immunomodulative effect of statins. In the Noel et al. analysis [29,30], containing the reports from the years 1966–2005, 28 statin dependent disease occurrence of autoimmune origin was described including; 10 SLE cases, 3 cutaneous lupus cases, 14 dermatomyositis cases and multiyosistis and pemphigoid case. In addition, in 2 SLE patients autoimmune hepatitis occurred [31]. Moreover, in some of those individuals antinuclear antibodies, which persisted for several months after clinical symptoms resolution, were observed. Statins administration is therefore not free of adverse reactions.

Statins effect on bone metabolism

Through the inhibition of hydroxymethylglutaryl coenzyme A transformation into mevalonian, statins unspecifically inhibit the transformation of farnesyl phosphate. The mechanism of this effect resembles the effect of bisfosfonians, which inhibit the transformation of mevalonian to farnesyl pyrophosphate. In the in vitro and in vivo studies, the statins' influence on osseal metabolism, through the increase in bone formation, as well as through bone tissue resorption inhibition, has been demonstrated. This happens through increased bone morphogenetic protein type II (BMP-2) gene expression in bones, the BMP-2 mRNA promotor region activation. The decrease in the Rho p21 protein prenylation responsible for the binding of guanosine triphosphate increases the osteogenesis, which results in bone formation intensification. In osteoclasts on the contrary, the inhibition of the protein isoprenylation, necessary for activation leads to its apoptosis. Another documented mechanism of bone mass increase is the role of nitric monoxide. Statins activate the Akt protein kinase, thus increasing nitric monoxide endothelial synthesis [32]. Such effects have previously been demonstrated in the in vitro studies and in animals, however now there is already strong evidence for a similar effect in humans. It is mainly the lipofilic statins that exert an effect on bone metabolism.

Data regarding clinical influence of statins on bone metabolism in terms of increased bone mineralization and fracture risk reduction are ambiguous. Two comparable retrospective studies of this issue demonstrated different results; one demonstrated a significant reduction in fracture risk, the other did not demonstrate a beneficial effect of statins' therapy [33,34]. Analyses of both studies were based on general practitioners practice in Great Britain and both studies analyzed groups of 81,000 patients. The differences concerned taking account of factors perturbing the analysis; other drugs administration, cigarette smoking, lipid disorders, hormone replacement therapy and body mass index (BMI). Including BMI may partially explain these differences to a certain extent (obesity potentially protects against fracture through body mass increase and bone shock absorption with falls).

During clinical studies on secondary prevention of cardiovascular events , with the use of pravastatin (LIPID) [35] and simvastatin (4S) [36], no decrease in bone fracture risk was reported. A limitation to the interpretation of usefulness of both studies was the participation of patients with low fracture risk (mainly men) and the lack of differentiation between osteoporotic and traumatic bone fractures.

The benefit of statin use was clearly demonstrated by Chan et al. [37] in the study of 928 postmenopausal women, in whom a bone mineral density (spine and femur neck) increase of about 7–8 % was observed during the 4-year follow-up. A similar beneficial effect was confirmed by the retrospective study of Wanga et al. [38], in the United States, on a group of over 6,000 patients.

This study demonstrated a nearly 50% fracture risk reduction in individuals taking statins. A slightly lower risk reduction (32%) was demonstrated by Rejnmark et al. [39]; its rate increased proportionally with the duration of statin therapy; the reduction did not concern individuals taking hypolipemic drugs from other groups.

Retrospective studies require an especially cautious attention. In the Women's Health Initiative Observational Study [40], for example, with the participation of over 93,000 postmenopausal women, statins were used in the older group, often with greater BMI, more often with previous myocardial infarction, and in women taking diuretics, and less often in individuals on hormone replacement therapy. A decrease in fracture risk was not confirmed in individuals on statins.

The diversity of study results assessing the alteration of bone fracture risk includes the BMI assessment as an evident factor of fracture risk. In Rejnmark's randomized study with the use of simvastatin in women with postmenopausal osteopenia, the BMI alterations and the bone turnover markers were assessed. [39]. In the 1- year follow-up a slight increase in BMI as well as a slight differentiation of bone turnover markers in the studied and control groups, were demonstrated.

Recently, two large meta-analyses were performed, one by Bajer et al. in 2004 [41] and other by Hatzigeorgiou et al. in 2005 [42]. Both of them included prospective observational and clinical randomized studies. In conclusion, statistically significant fracture risk decrease and bone mass density increase in the femur neck (only in retrospective studies) and the lack of such a relation for the lumbar spine were reported.

Experimental studies demonstrate a beneficial effect of statins on bone metabolism (including the anabolic effect), which has not however been confirmed in clinical studies. The reason for these differences is believed to be the low absorbency of statins in the intestines and the first pass through the liver effect, which in total leads to low statin bone tissue availability. It cannot however be excluded that in a broader perspective statins may contribute to the decrease in fracture risk.

SUMMARY

At present there is no reliable data allowing the intiation of statin administration as part of standard complementary therapy in rheumatic diseases. The pharmacotherapy indications in rheumatic diseases (after lipid profile assessment) are the same as those in the general population, therefore statin administration in chronic inflammatory diseases and hyperlipidemia is, in our opinion, justified.

Results of studies with use of specific agents suggest their usefulness in certain diseases. It is known that pravastatin is not appropriate for patients with osteoporosis and those with rheumathoid arthritis, atorvastatin seems to be the optimal choice, as already successfully administered in several studies [43].

The common use of statins and their indications that are clearly stated and not raising doubts (as cardiovascular diseases) will provide validation of their usefulness and the assessment of their safety in a large group of rheumatic disease

patients. This is suggested by the attempts to make analysis from the point of view of bone metabolism in clinical studies, which originally have been planned with a completely different aim.

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